

ONLINE SUPPLEMENT

Title:

Cerebral small vessel disease burden is increased in systemic lupus erythematosus.

Authors:

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Table I Scanning parameters

56 slices, 24 FOV, Top to bottom (start 1 slice above brain tissue), Straight axials (not AC-PC),

DTI = set fft_xsize + fft_ysize =128 and note locations.

SEQ. NUMBER	1	2	3	4	5	6	7	8	9
SEQUENCE	Loc	FLAIR	T2	GRE	Sag T2 Cube	3D IR PREP	DTI (32 directions)	FSPGR 2	FSPGR 12
ORIENTATION		AX	AX	AX	SAG	COR	AX	AX	AX
TE		140	102	14		MIN/FUL	MIN	MIN FULL	MIN FULL
TR		9400	8750	1420	3000		13750		
TI/prep time		2350				500			
FOV		24	24	24	24	24	24	24	24
SLICE THICK.		5	2.5	2.5	1	1.3	2.5	2.5	2.5
SLICE GAP		0	0	0	0	0	0	0	0
Acq. MATRIX		384 x 256	384 x 384	384 x 256	320 x 320	192 x 192	96 x 96	128 x 128	128 x 128
Padded (R x C)		512 x 512	512 x 512	512 x 512	512 x 512	256 x 256	128 x 128	256 x 256	256 x 256
Pixel width		0.47	0.47	0.47	0.47	0.94	1.875	0.94	0.94
Pixel height		0.47	0.47	0.47	0.47	0.94	1.875	0.94	0.94
Voxel depth		5	2.5	2.5	1	1.3	2.5	2.5	2.5
Resolution		2.133 pix/mm	2.133 pix/mm	2.133 pix/mm	2.133 pix/mm	1.067 pix/mm	0.533 pix/mm	1.067 pix/mm	1.067 pix/mm
PHASE FOV			1	1		1	1	1	1
FREQ. DIR		AP	AP	AP		SI	RL	AP	AP
BAND WIDTH		15.63	20.83	12.50		15.63		27.78	27.78
NEX		1	1	1	1	1	1	1	1
FLIP ANGLE				20		8		2	12
NO. SLICES		28	56	56	1 SLAB (180 locs)	1 SLAB (160 locs)	56	1 SLAB (62 locs)	1 SLAB (62 locs)
TIME of ACQ.	0:10	6:16	5:59	6:09	5:13	8:12	8:15	00:49	00:49

Brain Research Imaging Centre, University of Edinburgh. 2104. www.bric.ed.ac.uk

Table II Blood results for 51 SLE patients

	N (%) or mean \pm SD or median (Q1–Q3)	Reference range
Rheumatological		
C3 (mg / dL) (n=47)	1.2 \pm 0.32	0.81–1.57
C4 (mg / dL) (n=47)	0.19 \pm 0.09	0.13–0.39
Anti-ds-DNA (IU / mL) (n=47)	15 (8.5–33)	0–20
Inflammatory		
ESR (mm / hr) (n=49)	13 (6–21)	3–15
CRP (mg / L) (n=46)	2 (1–8)	0–5
IL-6 (pg / mL) (n=40)	1.72 (1.12–2.37)	
IFN (RQ value) (n=25)	6.7 (0.60–18.5)	
Endothelial dysfunction		
vWF Ag (IU / mL) (n=46)	1.71 \pm 0.66	0.42–1.22
vWF fVIIIc (IU / mL) (n=46)	1.38 \pm 0.45	0.5–1.5
vWF RCOF (IU / mL) (n=46)	1.37 \pm 0.41	0.42–1.22
Homocysteine (umol / L) (n=45)	17 (15–21)	0–20
Lipids		
Total cholesterol (mmol / L) (n=49)	5.02 \pm 0.95	<5.2
HDL cholesterol (mmol / L) (n=47)	1.42 \pm 0.41	>1
LDL cholesterol (mmol / L) (n=46)	2.96 \pm 0.84	<3.3
Antibodies		
Anti-cardiolipin IgG (GPL) (n=50)	3.35 (2.20–5.60)	0–13.3
Anti-cardiolipin IgM (MPL) (n=50)	1.65 (1.10–3.30)	0–9.8
Lupus anticoagulant (n=47)	5 positive	Positive/Negative

Anti-ds-DNA = anti-double stranded DNA, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HDL = high density lipoprotein, IFN = interferon, IgG = immunoglobulin isotype G, IgM = immunoglobulin isotype M, IL-6 = interleukin-6, LDL = low density lipoprotein, vWF Ag = von Willebrand Factor antigen, vWF fVIIIc = von Willebrand Factor factor VIIIc, vWF RCOF = von Willebrand Factor ristocetin co-factor

Table III Univariate and multivariable associations between total SVD score and other variables in SLE patients

	Unadjusted		Age adjusted		Adjusted for age and SLE disease duration	
	OR	95%CI	OR	95%CI	OR	95%CI
Vascular risk factors						
Age (years)	1.05	1.01 – 1.09 *	--	--	1.05	1.00 – 1.10 *
Hypertension (classified)	1.82	1.13 – 2.93 *	1.58	0.95 – 2.63	1.58	0.95 – 2.63
BMI (kg / m ²)	0.97	0.89 – 1.06	0.95	0.87 – 1.04	0.95	0.87 – 1.04
Disease duration (months)	1.00	0.99 – 1.01	1.00	0.99 – 1.00	--	--
Current smoker (Yes/No)	0.91	0.15 – 5.29	1.19	0.19 – 7.32	1.22	0.19 – 7.55
Ever smoked (Yes/No)	2.06	0.63 – 6.80	2.00	0.67 – 6.62	2.01	0.60 – 6.76
Steroids (Yes/No)	0.63	0.18 – 2.16	0.62	0.18 – 2.14	0.62	0.18 – 2.13
Neurological						
Fatigue	0.68	0.47 – 0.98 *	1.04	0.99 – 1.08	1.00	0.99 – 1.00
Anxiety	0.97	0.87 – 1.08	1.02	0.90 – 1.14	1.02	0.90 – 1.14
Depression	0.97	0.85 – 1.09	1.01	0.88 – 1.15	1.01	0.88 – 1.15
MMSE	0.94	0.63 – 1.38	1.05	0.69 – 1.58	1.07	0.69 – 1.67
MoCA	1.06	0.89 – 1.26	1.11	0.92 – 1.33	1.12	0.93 – 1.36
ACER	1.01	0.94 – 1.09	1.02	0.95 – 1.11	1.03	0.95 – 1.12
Rheumatology scores						
SLEDAI-2K	1.01	0.78 – 1.30	1.01	0.78 – 1.31	1.01	0.78 – 1.31
BILAG	0.95	0.85 – 1.07	0.98	0.87 – 1.11	0.99	0.87 – 1.11
SLICC	1.14	0.68 – 1.91	0.93	0.53 – 1.62	0.88	0.48 – 1.65
DTI biomarkers						
MD across 12 tracts (n=47)	2.58	1.32 – 5.06 †	2.32	1.16 – 4.64 *	2.53	1.22 – 5.22 *
FA across 12 tracts (n=47)	0.42	0.22 – 0.80 †	0.47	0.24 – 0.93 *	0.43	0.21 – 0.88 *
Bloods						
C3 (mg / dL) (n=47)	1.06	0.15 – 7.56	1.06	0.14 – 8.11	1.14	0.14 – 8.93
C4 (mg / dL) (n=47)	1.07	0.52 – 2.20	1.14	0.55 – 2.35	1.17	0.56 – 2.47
Anti-ds-DNA (IU / mL) (n=47)	0.99	0.98 – 1.01	0.99	0.98 – 1.00	0.99	0.98 – 1.01
ESR (mm / hr) (n=49)	1.03	0.99 – 1.06	1.02	0.98 – 1.06	1.02	0.98 – 1.06
CRP (mg / L) (n=45)	0.99	0.92 – 1.08	0.99	0.92 – 1.08	1.00	0.92 – 1.08
IL-6 (pg / mL) (n=40)	0.99	0.71 – 1.40	1.02	0.72 – 1.43	1.02	0.72 – 1.43
IFN (RQ value) (n=24)	1.04	0.94 – 1.14	1.04	0.95 – 1.14	1.04	0.93 – 1.16
vWF Ag (IU / mL) (n=46)	1.21	0.48 – 3.00	0.88	0.33 – 2.30	0.87	0.33 – 2.31
vWF F8c (IU / mL) (n=46)	2.50	0.66 – 9.45	2.30	0.62 – 8.57	2.31	0.62 – 8.61
vWF RCOF (IU / mL) (n=46)	2.00	0.46 – 8.56	1.24	0.26 – 5.83	1.25	0.26 – 5.91
Homocysteine (umol / L) (n=45)	1.03	0.94 – 1.12	1.01	0.92 – 1.11	1.01	0.92 – 1.11
Tot cholesterol (mmol / L) (n=49)	1.55	0.84 – 2.87	1.37	0.72 – 2.59	1.38	0.73 – 2.62
HDL cholesterol (mmol / L) (n=47)	1.35	0.32 – 5.74	1.41	0.33 – 6.04	1.39	0.32 – 6.02
LDL cholesterol (mmol / L) (n=46)	1.72	0.85 – 3.49	1.47	0.71 – 3.01	1.50	0.71 – 3.14
Anti-cardiolipin IgG (GPL) (n=50)	0.92	0.77 – 1.09	0.93	0.78 – 1.11	0.93	0.78 – 1.10
Anti-cardiolipin IgM (MPL) (n=50)	1.00	0.95 – 1.06	0.98	0.93 – 1.04	0.98	0.93 – 1.04
Lupus anticoagulant (n=47)	0.42	0.06 – 2.73	0.30	0.04 – 2.18	0.30	0.04 – 2.15

* p<0.05, † p<0.01

ACER = Addenbrooke's Cognitive Examination – Revised, BMI = body mass index, BILAG = British Isles Lupus Assessment Group, BTV = brain tissue volume, CRP = C-reactive protein, DTI = diffusion tensor imaging, ESR = erythrocyte sedimentation rate, FA = fractional anisotropy, HDL = high density lipoprotein, LDL = low density lipoprotein, MD = mean diffusivity, MMSE = Mini Mental State Examination, MoCA = Montreal Cognitive Assessment, IFN = interferon beta, IL-6 = interleukin-6, ICV = intracranial volume, SLEDAI-2K = systemic lupus erythematosus Disease Activity Index, SLICC = Systemic Lupus International Collaborating Clinics, vWF Ag = von Willebrand Factor antigen, vWF F8c = von Willebrand Factor VIII, vWF RCOF = von Willebrand Factor ristocetin co-factor

Table IV Unadjusted univariable associations between individual SVD features and other variables in SLE patients

	PVS BG		PVS CS		WMH (Total Fazekas)	
	OR	95%CI	OR	95%CI	OR	95%CI
Vascular risk factors						
Age (years)	1.02	0.98 – 1.06	1.03	0.99 – 1.07	1.13	1.07 – 1.20 ‡
Hypertension (classified)	1.36	0.90 – 2.05	1.25	0.84 – 1.86	1.88	1.20 – 2.94 †
BMI (kg / m ²)	0.97	0.89 – 1.05	0.98	0.91 – 1.07	1.03	0.95 – 1.25
Disease duration (months)	1.00	0.99 – 1.00	1.00	0.99 – 1.00	1.00	0.99 – 1.00
Current smoker (Yes/No)	0.87	0.19 – 3.92	0.50	0.11 – 2.34	1.87	0.37 – 9.40
Ever smoked (Yes/No)	0.82	0.30 – 2.23	0.77	0.27 – 2.18	2.63	0.87 – 7.89
Steroids (Yes/No)	0.48	0.17 – 1.41	0.74	0.25 – 2.24	1.44	0.47 – 4.36
Rheumatology scores						
SLEDAI	1.10	0.88 – 1.37	1.04	0.80 – 1.35	1.00	0.78 – 1.29
BILAG	0.96	0.86 – 1.07	0.93	0.84 – 1.04	0.96	0.86 – 1.07
SLICC	0.86	0.55 – 1.35	0.92	0.57 – 1.49	1.42	0.88 – 2.28
Bloods						
C3 (mg / dL) (n=47)	0.35	0.06 – 1.98	1.08	0.22 – 5.29	0.70	0.13 – 3.71
C4 (mg / dL) (n=47)	0.85	0.45 – 1.62	1.16	0.64 – 2.09	0.79	0.42 – 1.49
Anti-ds-DNA (IU / mL) (n=47)	1.00	0.99 – 1.02	1.00	0.99 – 1.01	1.00	0.99 – 1.01
ESR (mm / hr) (n=49)	1.02	0.98 – 1.05	0.99	0.96 – 1.02	1.03	0.99 – 1.06
CRP (mg / L) (n=45)	1.00	0.99 – 1.03	1.02	0.98 – 1.06	1.02	0.99 – 1.04
IL-6 (pg / mL) (n=40)	1.04	0.79 – 1.37	0.94	0.71 – 1.24	0.98	0.74 – 1.29
IFN (RQ value) (n=24)	0.93	0.86 – 1.00	0.97	0.91 – 1.05	0.98	0.90 – 1.06
vWF Ag (IU / mL) (n=46)	0.96	0.43 – 2.17	1.56	0.67 – 3.60	1.30	0.56 – 2.99
vWF F8c (IU / mL) (n=46)	1.39	0.40 – 4.84	2.58	0.69 – 9.64	1.89	0.54 – 6.63
vWF RCOF (IU / mL) (n=46)	1.07	0.29 – 3.89	1.62	0.42 – 6.21	1.34	0.31 – 5.76
Homocysteine (umol / L) (n=45)	0.97	0.89 – 1.04	1.02	0.94 – 1.11	1.07	0.98 – 1.16
Tot cholesterol (mmol / L) (n=49)	1.75	0.98 – 3.12	1.40	0.80 – 2.46	1.31	0.73 – 2.35
HDL cholesterol (mmol / L) (n=47)	3.30	0.86 – 12.6	14.8	2.76 – 80.0 ‡	0.95	0.23 – 3.99
LDL cholesterol (mmol / L) (n=46)	1.89	0.96 – 3.71	1.11	0.58 – 2.12	1.38	0.70 – 2.73
Anti-cardiolipin IgG (GPL) (n=50)	1.00	0.86 – 1.16	0.94	0.80 – 1.09	0.88	0.75 – 1.04
Anti-cardiolipin IgM (MPL) (n=50)	1.02	0.97 – 1.08	1.02	0.97 – 1.07	0.99	0.94 – 1.04
Lupus anticoagulant (n=47)	0.79	0.14 – 4.67	1.23	0.22 – 6.84	0.60	0.11 – 3.22

* p<0.05, † p<0.01 ‡ p<0.0001

BMI = body mass index, BILAG = British Isles Lupus Assessment Group, BTV = brain tissue volume, CI = confidence interval, CRP = C-reactive protein, DTI = diffusion tensor imaging, ESR = erythrocyte sedimentation rate, HDL = high density lipoprotein, LDL = low density lipoprotein, IFN = interferon beta, IL-6 = interleukin-6, ICV = intracranial volume, OR = odds ratio, PVS BG = perivascular spaces in basal ganglia, PVS CS = perivascular spaces in centrum semiovale, SLEDAI = systemic lupus erythematosus Disease Activity Index, SLICC = Systemic Lupus International Collaborating Clinics, vWF Ag = von Willebrand Factor antigen, vWF F8c = von Willebrand Factor VIII, vWF RCOF = von Willebrand Factor ristocin co-factor, WMH = white matter hyperintensities

Table V Imaging biomarkers of SVD in SLE and NPSLE patients

	SLE	NPSLE	
	Median (Q1–Q3)	Median (Q1–Q3)	p value
N	47	4	
Lacunae	0 (0–0)	0 (0–0)	0.52
Microbleeds	0 (0–0)	0 (0–0)	0.71
PVS BG (score 0–4)	2 (2–3)	2.5 (1.5–3.0)	0.76
PVS CS (score 0–4)	3 (3–4)	3.0 (1.5–4.0)	0.72
WMH periventricular (score 0–3)	1 (1–1)	1.5 (0.5–2.5)	0.43
WMH deep (score 0–3)	1 (0–1)	1.5 (1.0–2.5)	0.04 *
WMH (total Fazekas score 0–6)	2 (1–2)	3.0 (1.5–5.0)	0.22
Total SVD score (score 0–4)	1 (1–2)	1.5 (1.0–3.5)	0.43
Deep atrophy (score 1–6)	1 (1–2)	1.5 (1.0–2.5)	0.49
Superficial atrophy (score 1–6)	1 (1–1)	1.5 (0.5–2.0)	0.59

* p<0.05

BG = basal ganglia, CS = centrum semiovale, NPSLE = neurropsychiatric SLE, PVS = perivascular spaces, SVD = small vessel disease, SLE = systemic lupus erythematosus, WMH = white matter hyperintensities.

Medications

Fifty of 51 SLE patients were taking one or more regular medications for SLE at time of MR scanning, including non-steroidal anti-inflammatory drugs (n=2 SLE patients); anti-malarials (n=40); immunosuppressants (n=30); corticosteroids (n=18); and biological therapy (n=1). Additionally, one patient was on warfarin, several were on alendronic acid for osteoporosis and many were taking pain killers as required. We cross-checked these self-reported medications with records from rheumatology / the NHS.